

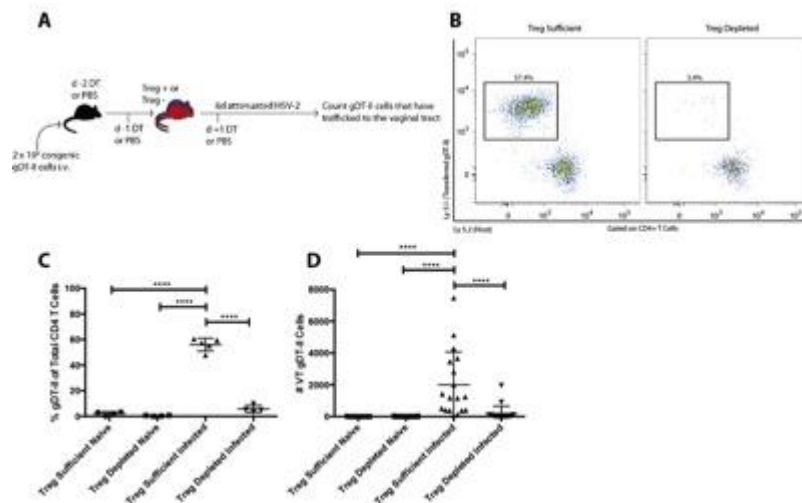
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SCIENCE SPOTLIGHT

Beyond suppression: function of regulatory T cells in herpes infection

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Experimental layout and results showing that mice lacking regulatory T cells at the time of intravaginal HSV-2 infection have a greatly diminished antigen-specific CD4 T cell response in comparison to wild type mice. This surprising difference helps explain why the mice without regulatory T cells do not control the viral infection as well as expected.

Figure provided by Dr. Andrew Sorensen.

Regulatory T cells (Tregs) are named for their first recognized function of controlling the immune response in homeostatic conditions, thereby avoiding autoimmunity, as well as to prevent an excessive immune response during and following an infection. In some infections, such as herpes simplex virus-1 (HSV-1), *Pneumocystis carinii* and *Leishmania major*, lack of Tregs results in a more robust immune response. However, this is not applicable to all cases. Paradoxically, efficient immune responses against respiratory syncytial virus (RSV) and *Candida albicans* require the presence of Tregs. In a similar fashion, Treg depletion was shown to affect the early innate immune response in a mouse model of genital herpes simplex virus-2 (HSV-2) (Lund et al., *Science* 2008). Can Tregs also influence the adaptive immune response? If so, how? In a paper published last month in the journal *Mucosal Immunology*, Dr. Andrew Soerens, recently graduated from the Lund Lab in the Vaccine and Infectious Disease Division at Fred Hutch, addressed in detail these two questions.

Starting with the finding that HSV-2-specific T cells fail to accumulate in the vaginal tract of Treg-depleted HSV-2-infected mice (as shown in the figure), the paper leads us backward to find the cause of such impairment. In normal conditions, upon infection antigens are carried to draining

lymph nodes by specialized cells, called dendritic cells (DC), and presented to T cells, inducing antigen-specific T cells to undergo clonal proliferation and migration to the infected tissue. Therefore, the observed disruption in the process that leads to a lack of antigen-specific T-cell accumulation in the vaginal tract upon HSV-2 infection could result from defects at different stages in antigen processing or T cell response. The finding that the absence of Tregs not only impairs such accumulation at the tissue level, but also in the blood, points toward an inefficient T cell activation, expansion or egress of activated T cells from the draining nodes. Treg deficiency led to a failed activation of T cells; moreover, when Tregs were depleted after T cell priming was completed, the number of HSV-2 specific T cells in the blood and the vaginal tract were comparable to that observed in the presence of Tregs, showing the importance of Treg in T-cell priming. In particular, Tregs were needed for dendritic cell trafficking from the vaginal tract to the draining lymph node, guided by the chemokine CCL-21, whose levels were decreased in the absence of Tregs. A key molecule in this process was found to be CTLA-4, as its lack of expression on Tregs recapitulated the same phenotype observed for Treg-deficiency. Lack of CTLA-4, which inhibits T cell activation by binding two co-receptors on the cell surface, might result in non-specific T-cell proliferation in the lymph node and cause an inflammatory environment that had been previously shown to be responsible for reduced levels of CCL21.

Obviously, there is more to Tregs than suppressing the immune response. "This research helps to reveal an unappreciated reason why regulatory T cells are important. It has been known for many years that regulatory T cells are needed to prevent autoimmunity, but this research highlights that in some contexts, regulatory T cells are actually needed to keep the immune system in a state where it is capable of mounting an appropriate response against a pathogen" concluded Dr. Soerens, now in Minnesota, as we send him our best wishes on his postdoctoral adventure!

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[Soerens AG, Da Costa A, Lund JM.](#) 2016. Regulatory T cells are essential to promote proper CD4 T-cell priming upon mucosal infection. *Mucosal Immunol.* doi: 10.1038/mi.2016.19. [Epub ahead of print]